

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 01736	International filing date (day/month/year) 05/05/2000	(Earliest) Priority Date (day/month/year) 07/05/1999
Applicant THE UNIVERSITY OF LIVERPOOL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

THERAPEUTIC USE OF AN INHIBITOR OR AN ANTAGONIST OF AN ABC PROTEIN IN BONE

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-16,19,20

A compound which will act as an inhibitor or antagonist of an ABC protein in bone for use in the manufacture of a medicament for use in the treatment of a disease where full or partial inhibition of bone resorption will result in an improvement of the disease, a composition comprising such an inhibitor together with parathyroid hormone and a method of treatment by means of the aforementioned compound/composition.

2. Claims: 17,18

A method of screening for a compound which acts as an inhibitor or antagonist of the expression or function of an ABC protein.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,3-16, 19, 20 relate to a compound and a composition defined by reference to a desirable characteristic or property, namely "an inhibitor or an antagonist of an ABC protein in bone". The claims cover all compounds and compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds and compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds and compositions by reference to their pharmacological profiles. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, present claims 1-16, 19-20 relate to the treatment of a disease which actually is not well defined. The use of the definition "a disease where full or partial inhibition of bone resorption will result in an improvement of the disease" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in claim 2 and the diseases mentioned in the description, p. 1, namely osteopenia, osteoporosis, Paget's disease, bone metastases, myeloma, periodontal disease and humoral hypercalcaemia of malignancy, with due regard to the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No.

GB 00/01736

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/64 A61P19/08 A61P19/10 A61K38/29 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CANCERLIT, AIDSLINE, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 861 666 A (TAKEDA CHEMICAL INDUSTRIES LTD) 2 September 1998 (1998-09-02) abstract page 3, line 16 - line 55 page 9, line 42 - line 55 page 10, line 3 - line 6 page 11, line 7 - line 20 page 12, line 1 - line 24 page 13, line 16 - line 50 claims 15,25-29 ---	1-8,19
X	E. F. REYNOLDS: "Martindale - The Extra Pharmacopoeia Thirty-first edition" 1996, ROYAL PHARMACEUTICAL SOCIETY, LONDON XP002151468 224540 page 346, column 1 -page 348, column 2 page 360, column 2 -page 361, column 2 --- -/--	1-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

26 March 2001

Date of mailing of the international search report

05. 04. 2001

Name and mailing address of the ISA

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Griffith, G

INTERNATIONAL SEARCH REPORT

International Application No

GB 00/01736

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GOLSTEIN P E, BOOM A, VAN GEFFEL J, JACOBS P, MASEREEL B, BEAUWENS R: "P-glycoprotein inhibition by glibenclamide and related compounds." PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, vol. 437, no. 5, April 1999 (1999-04), pages 652-660, XP000951466 abstract page 652, column 2, paragraph 2 -column 1, paragraph 1 page 658, column 1, paragraph 3 page 659, column 1, paragraph 4 ---</p>	1,2
X	<p>Y HAMMON, M-F LUCIANI, F BECQ, B VERRIER, A RUBARTELLI AND G CHIMINI: "Interleukin-1beta secretion is impaired by inhibitors of the Atp binding cassette transporter, ABC1." BLOOD, vol. 90, no. 8, 15 October 1997 (1997-10-15), pages 2911-2915, XP000939111 abstract page 2911, column 1, paragraph 3 -column 2, paragraph 2 page 2914, column 1, paragraph 1 ---</p>	1,2
X	<p>COULSON R; MOSES A M: "EFFECT OF CHLORPROPAMIDE ON RENAL RESPONSE TO PARATHYROID HORMONE IN NORMAL SUBJECTS AND IN PATIENTS WITH HYPO PARATHYROIDISM" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 194, no. 3, 1975, pages 603-613, XP000951483 abstract page 604, column 2, paragraph 1 - paragraph 3 figure 1 page 611, column 2, paragraph 3 -column 1, paragraph 1 ---</p>	10-16
X	<p>DAVIES T F, PRUDHOE K: "Parathyroid hormone and adenylate cyclase." LANCET, vol. 1, no. 7955, 1976, page 363 XP000937577 the whole document --- -/--</p>	10-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

GB 00/01736

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0861666	A	02-09-1998	AU 723097 B	17-08-2000
			AU 5603496 A	09-01-1997
			CA 2179584 A	21-12-1996
			CN 1145783 A	26-03-1997
			CZ 9601811 A	15-01-1997
			EP 0749751 A	27-12-1996
			HU 9601698 A	28-05-1997
			JP 9067271 A	11-03-1997
			JP 10167986 A	23-06-1998
			NO 962606 A	23-12-1996
			NO 20004345 A	23-12-1996
			SK 79496 A	08-01-1997
			US 5965584 A	12-10-1999
			US 6150383 A	21-11-2000
			US 6133293 A	17-10-2000
			US 6166042 A	26-12-2000
			US 6166043 A	26-12-2000
			US 6150384 A	21-11-2000
			US 6121295 A	19-09-2000
			US 6156773 A	05-12-2000
			US 6174904 B	16-01-2001
			US 6121294 A	19-09-2000
			US 6080765 A	27-06-2000
			US 6133295 A	17-10-2000
			US 6103742 A	15-08-2000
			US 5952356 A	14-09-1999
WO 9837764	A	03-09-1998	AU 6538698 A	18-09-1998
			EP 0989805 A	05-04-2000

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REC'D 17 JUL 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference xxxx	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01736	International filing date (day/month/year) 05/05/2000	Priority date (day/month/year) 07/05/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant THE UNIVERSITY OF LIVERPOOL		


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 06/12/2000	Date of completion of this report 13.07.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Beeck, M Telephone No. +49 89 2399 8473



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01736

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-13 as originally filed

Claims, No.:

1-20 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ ~~contained in the international application in written form.~~
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01736

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-20.

because:

☒ the said international application, or the said claims Nos. 17-20 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

-
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

SECTION III:

Claims 17 to 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the **industrial applicability** of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION IV:

The subject-matter of independent claims 1 and 19 is already known (see the grounds for this objection). The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the following groups of inventions:

1. Claims 1-16, 19 and 20 (invention 1):

Compounds comprising an inhibitor or antagonist of an ABC protein and their use in the treatment of a disease where inhibition of bone resorption will result in an improvement in the disease.

2. Claims 17 and 18 (invention 2):

Screening method for a compound which will act as an inhibitor or antagonist of the expression or function of an ABC protein in bone.

The non-unity objection could only be met by restricting the application to one of the two inventions.

Only the first invention has been examined (Article 34 (3) (c), first sentence).

SECTION V:

- 1) The documents are numbered according to their sequence in the search report.

- 2) Document D1 already describes pharmaceutical compositions comprising glibenclamide (see working example 2, experimental example 2 and claim 25), also for the treatment of osteopenia.

Document D9 describes the treatment of osteoporosis with glibenclamide.

Document D2 discloses pharmaceutical compositions of chlorpropamide, glibenclamide, gliclazide, glipizide, gliquidone, tolazamide and tolbutamide.

Therefore the subject-matter of claims 1 to 9 and 19 is not novel.

- 3) Since documents D5 to D7 do not provide pharmaceutical compositions comprising chlorpropamide and parathyroid hormone, but merely disclose tests which besides are not related to bone resorption, the subject-matter of claims 10 to 16 and 20 was not obvious for the person skilled in the art, so that it involves an inventive step.
- 4) For the assessment of the present claims 17 to 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
-

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 January 2001 (15.01.01)	
International application No. PCT/GB00/01736	Applicant's or agent's file reference
International filing date (day/month/year) 05 May 2000 (05.05.00)	Priority date (day/month/year) 07 May 1999 (07.05.99)
Applicant GALLAGHER, James, Anthony et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

06 December 2000 (06.12.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

US 0998071703P1



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Indexing Officer: FDEBESAI - FISSEHA DEBESAI
Team: OIPEBackFileIndexing
Dossier: 09980717

Legal Date: 11-02-2002

No.	Doccode	Number of pages
1	M905	2

Total number of pages: 2

Remarks:

Order of re-scan issued on